HISTAMINE IN ANAPHYLAXIS AND ALLERGY*

LAURENCE FARMER

Associate in Medicine, Lenox Hill Hospital

THE application of immunological concepts to the study of the idiosyncrasies has formed the foundation for a sound scientific approach to these baffling conditions. The discovery of anaphylaxis and the assumption that idiosyncratic diseases are anaphylactic conditions, have been of great importance. The conception that allergic diseases (as they are called today) are "anaphylactic" diseases, in other words that allergy is "human anaphylaxis," has led to a heated controversy of long standing. The one school of thought contends that clinical allergy and experimental anaphylaxis, although resembling one another in certain respects, are fundamentally different conditions; the other school, to which I belong, believes with Hans Zinsser[1] that allergy in man "is based on an immunological mechanism basically identical with anaphylaxis in animals, superficially modified by human anatomical and physiological conditions."

Notwithstanding these theoretical differences of opinion, the practical approach to the therapy of allergic diseases elaborated on the basis of these immunological concepts is to combat them by specific desensitization with the causative allergen or allergens. This immunological approach has been very successful, and one can be well satisfied with the results when one compares the relative helplessness of former days with our present therapeutic achievements. More and more allergens have been discovered; more and more allergenic extracts are being used in the treatment of allergic diseases.

However, there are some of us who have become perturbed by this ever expanding multiplicity of allergens and who have striven towards reducing the treatment of allergic diseases to a common denominator; that is, we have aimed at non-specific treatment as opposed to specific desensitization. Many attempts have been made to this end; some of

* Read April 16, 1940 before the Section of Medicine of The New York Academy of Medicine.
From the Allergy Clinic, Lenox Hill Hospital.

them were comparatively successful; few of them, however, could compare with specific desensitization in practical achievement; only one of them compares in theoretical soundness. It is this latter attempt and especially its theoretical foundation that I should like to discuss this evening.

Anaphylaxis and the recognition of its importance as a biological principle were first described in 1902 by Richet.[2] It was shown that re-injection of an antigen into an animal, after the lapse of an incubation period, led to dramatic symptoms, which were termed anaphylactic shock. During the following years various theories were advanced to explain the symptomatology of anaphylactic shock. However, none of them was really satisfactory. Not even the anaphylatoxin-theory, one of the most generally accepted ones, was able to explain satisfactorily the phenomena of anaphylactic shock.

In a paper on the physiological action of histamine, Dale and Laidlaw[3] stated in 1910: "We content ourselves with recording as a point of interest and possible significance, the fact that the immediate symptoms with which an animal responds to an injection of a normally inert protein, to which it has been sensitized, are to a large extent those of poisoning by beta-iminazolyl-ethylamine."

This was one of those bold conceptions of a genius which, conceived at a time when there were hardly any tangible facts on which to base them, prove to have been correct after years of painstaking labor. Later experiments on anaphylaxis led Dale[4] to the conclusion that "the symptoms of the anaphylactic reaction" are due, "not to the formation of a poison in the blood but to the reaction between the antigen and a precipitating antibody located in the cell protoplasm."[5] He further called attention to the close similarity between the anaphylactic responses of different tissues in various species of animals and the responses of those particular tissues to histamine; the symptoms of anaphylactic shock in the various species are the symptoms of histamine shock in each species. In different species these symptoms are determined by the reactions of different organs which have been termed "shock organs." Thus the shock organ in the dog is the liver, in the guinea pig the lungs.

There is, furthermore, considerable though not complete parallelism between the histamine sensitivity of a species and its anaphylactic response.[6] On the one hand the guinea pig, which is highly sensitive to histamine, is eminently susceptible to anaphylactic shock; on the other

hand the rat, which is highly resistant to histamine, cannot be made anaphylactic under normal circumstances.[7]

Histamine is the amine produced by decarboxylation of the amino-acid histidine. Its principal physiological actions affect the circulation, the plain musculature and the secretory glands.[8] Its circulatory actions are a constrictor effect on the arterioles and a dilator effect on the capillaries. This dilatation so increases the permeability of the capillary wall that fluid passes out from the blood stream into the tissues. Its action on plain musculature leads to contraction of various organs such as the uterus and the gallbladder, and to intense constriction in others, as in the lungs. Its action on the secretory glands consists of stimulation of their activity.

Histamine was prepared synthetically in 1907 by Windaus and Vogt.[9] In 1910 Ackermann[10] obtained it by submitting histidine to the action of putrefactive bacteria, and in the same year Barger and Dale[11] discovered the presence of histamine in ergot. But there was no proof that histamine occurred in animal tissues and it was hard to understand how it could be formed almost instantaneously in the course of the anaphylactic reaction. In the following years several attempts were made to isolate histamine from animal tissues,[12] but it was not until 1927 that Best, Dale, Dudley and Thorpe[13] were able to show conclusively that this base was a normal constitutent of the liver and lungs. Later, many other tissues were also shown to contain histamine.[14]

In 1929 Dale[15] formulated his theory of anaphylaxis in the following words: "We may picture anaphylactic shock as the result of cell injury, due to the intracellular reaction of the antigen with an aggregating antibody. Whether this is general or localized in a particular organ, histamine will be released, and its effect will be prominent in the resulting reaction, imposing a general resemblance to the syndrome produced by histamine itself, on the symptoms seen in each species."

Up to this time there existed very little experimental evidence in support of Dale's theory, and the findings of Best and his co-workers naturally were of great importance. In the years preceding their discovery, other valuable contributions to the histamine theory had been made by Lewis and his associates. Lewis, who had described the so-called "triple response" of the human skin,[16] together with Grant compared the reaction of histamine and of fish extract in a fish-sensitive patient. Lewis and Grant[17] found that when histamine and a fish extract were

punctured simultaneously into this patient's skin, the resulting reactions were identical. That is, the fish extract also led to the threefold reaction. This reaction comprises:

1) a red spot of an approximately circular shape around the puncture due to local dilatation of the capillaries and venules;

2) a wheal over the same area due to a locally increased permeability of the vessel walls; and

3) a vivid scarlet flush, several centimeters in diameter, with irregular margins due to a reflex dilatation of the neighboring arterioles.

Lewis postulates that the triple response, which may be obtained by stimulation of the skin by chemical and by physical means such as heat, cold and light is caused by liberation in the skin of a histamine-like substance. Lewis and Grant conclude that the "anaphylactic poison" also acts on the skin by liberating in it an H-substance. Incidentally, Lewis' and Grant's paper is entitled "Notes on the anaphylactic skin reaction," not on the allergic skin reaction.

Hare's[18] findings were identical. He examined a pollen-sensitive and two horse-sensitive patients and found that horse extracts and pollen extracts also produced the three-fold skin reaction. These papers are especially important as they show that histamine plays a role in clinical allergy in humans and not only in experimental anaphylaxis in animals.

Between 1932 and 1939 a considerable number of workers adduced experimental evidence which leaves little doubt as to the correctness of Dale's theory. The following are the salient findings of these corroborative experiments:

1) During anaphylactic shock in the dog there appears in the blood and lymph a substance showing the biological characteristics of histamine.[19]

2) On perfusion of the isolated lungs of sensitized guinea pigs with a solution of the appropriate antigen there appears a histamine-like substance in the shock fluid which induces broncho-constriction in the lungs of normal guinea pigs.[20]

3) The active substance released during canine anaphylactic shock and from the shocked lungs of guinea pigs is inactivated by incubation with histaminase.[21]

4) A substance with the characteristics of histamine is released from various tissues of sensitized guinea pigs if the tissues are removed and shocked in vitro.[22]

5) Certain substances, which suppress the histamine contraction of plain musculature, also suppress their anaphylactic contraction. They do not, however, prevent the immunological stage of the reaction.[23]

6) During anaphylactic shock in dogs and guinea pigs there is a marked increase of the histamine content of the blood. In these latter experiments histamine was chemically identified as such.[24]

These findings cannot leave any doubt that histamine is released from the tissues during the anaphylactic reaction in animals and that it is responsible for the symptoms of anaphylactic shock.

For obvious reasons the evidence, which has been adduced to show that histamine is also responsible for the symptoms of clinical allergy, is more indirect and less comprehensive, but still very suggestive.

I have already mentioned the work of Lewis and his collaborators, in which they demonstrated that in atopic allergy the reaction of the skin to the specific allergen has all the earmarks of a reaction to histamine.

Certain individuals react to physical agents such as heat, cold, sunlight, with symptoms of hypersensitiveness such as asthma, vasomotor rhinitis, urticaria, angioneurotic edema.[25] This condition, which has been termed "physical allergy," is not based on an immunological mechanism. The work of Bray[26] and of Horton and his associates[27] has made it very probable that its symptoms are also caused by the liberation of preformed histamine from the tissues. In a boy suffering from cold allergy, Bray observed the triple response of Lewis, if the child's hands were immersed for a few minutes in water of 45 degrees Fahrenheit. In this experiment the patient's hands also became very itchy and swollen to more than twice their natural size. Several hours later the boy generally developed an irritating cough. In normal individuals Bray could provoke the characteristic triple response by immersion of the hands in water of 20 degrees Fahrenheit.

Horton, in collaboration with Roth and Brown,[27] described similar local and also systemic reactions to cold. The systemic reactions consisted of flushing of the face, a marked fall in blood pressure, a rise in pulse rate, and, frequently, development of syncope. Horton and Brown[28] further demonstrated that in a number of cold-sensitive individuals, immersion of the hand in water of 50 degrees Fahrenheit led to an increase of gastric acidity. Incidentally, Tinel[29] and his co-workers have reported increase of gastric acidity in serum-sensitive dogs on re-

injection of serum. All of the described reactions are typical reactions to histamine, and the assumption made by Bray and by Horton that these symptoms of physical allergy are caused by the liberation of histamine or of a histamine-like substance is very plausible.

As a point of special interest I should like to mention observations of Grant[30] and his co-workers, who were able to show that in cases of psychogenic urticaria the eruption was easily provoked by emotional stimuli, and also by exercise and warming the body. The explanation given by Grant is that, through stimulation of cholinergic nerve fibers, acetylcholine is released in the skin and that the acetylcholine in turn leads to liberation of a histamine-like substance.

In investigations on the pharmacological actions of pituitrin and its active constituents Fühner,[31] in 1912, found that it is possible to make rabbits tolerant to histamine. He injected increasing amounts and was able eventually to give doses which otherwise would have caused severe reactions. This observation was later to furnish the foundation for a new approach to the treatment of allergic diseases. Fühner's findings were verified and expanded by other workers[32] who were able to demonstrate that refractoriness to histamine can be induced also in other species, including humans.

The phenomenon of induced refractoriness to histamine has also furnished further proofs of the correctness of the histamine theory of anaphylaxis and allergy. In anaphylactic guinea pigs I[33] was able to show that the uterine strips of serum-sensitized animals, which had received histamine by injection or by mouth, were less sensitive to the specific antigen than were the sensitized uterine strips of the control animals, which had not received histamine. Miyamoto[34] had similar results.

In allergic humans Hare, whose work I previously mentioned, demonstrated that the skin of allergic individuals, if stimulated by the specific allergen, was rendered refractory alike to the allergen and to histamine. He further showed that if the skin was stimulated by histamine it was rendered refractory to the allergen.

We have traveled a long way since Dale in 1910 first recorded the belief—"as a point of interest and possible significance"—that the symptoms of anaphylactic shock are to a large extent those of poisoning by histamine.

The experimental observations, which since then have been made and which I have just presented to you, form the theoretical and prac-

tical basis of the histamine treatment of allergic diseases. The histamine theory would explain the symptoms of allergic conditions and why they are independent of the nature of the causative allergen and dependent only on the reaction of the shock organs. The possibility of inducing refractoriness to histamine, the substance responsible for the reaction of the shock organs, would reduce the treatment of allergic diseases to a common denominator.

Ramirez and St. George[35] were the first to use histamine in the treatment of an allergic condition. In 1924 they reported that they had used subcutaneous injections of histamine in the treatment of ten patients suffering from asthma due to "histamine sensitivity." These cases, which do not fit into the category of either atopic or physical allergy, remind one of the recent work of Horton[36] on "vascular headache." These headaches, which Horton attributes to histamine, are also alleviated by histamine injections.

In the sixteen years following Ramirez' and St. George's paper, there are but few reports in the literature on the use of histamine in allergic diseases. Friedlaender and Petow[37] applied it in various forms of migraine; Ernstene and Banks,[38] Gajdos,[39] Joltrain,[40] and Alexander and Elliot[41] used it in the treatment of urticaria; Collens and his associates[42] in the treatment of a case of insulin sensitivity.

Stahl and Masson,[43] Piquet,[44] Thiberge,[45] and Dzsinich[46] used histamine in the treatment of bronchial asthma. Thiberge used it also in hay fever.

Bray[26] was able to achieve disappearance of the symptoms in his case of allergy to cold by injections of histamine, and Horton and his coworkers[27] later reported similar good results in the treatment of physical allergy.

The number of cases treated by these various workers is comparatively small, the time of observation relatively short. All of the authors, however, were impressed by the results achieved with histamine.

If histamine could be used successfully in the treatment of allergic diseases it would make for much simplification. Its use would be especially indicated in cases of multiple sensitiveness, in which several allergens would have to be used for specific desensitization, and also in cases which might be on an allergic basis in spite of the fact that a causative allergen could not be discovered. The physical allergies, as Bray and Horton have indicated, should also be amenable to histamine treatment.

These practical considerations and the soundness of the histamine theory have made us feel that the value of histamine therapy in allergic conditions should be intensively investigated.

For more than three years we therefore have been using histamine phosphate in the treatment of asthma, vasomotor rhinitis and hay fever in my clinic at Lenox Hill Hospital. We have been giving it by subcutaneous injection and have been following Dzsinich's suggestion of using small doses. According to our opinion, the amounts used by the older workers (30 to 750 gammas per injection) are much too high. The initial dose in milder cases of asthma in adults is .1 gamma, in severe cases .01 gamma. In the preseasonal treatment of hay fever our initial dose has been .1 or 1.0 gamma. In children we always start with .01 gamma. In asthma and vasomotor rhinitis the maximum dose has been 50 to 75 gammas, in hay fever 100 to 200 gammas (in adults). The increase in dosage, the spacing of the injections and the number of injections given, depend on the patient's tolerance, age, and on the results achieved. Our detailed procedure and a discussion of our results and observations in asthma and vasomotor rhinitis are contained in a paper which is in press.[47]

The precautions to be taken are the same as in specific desensitization. However, we believe that histamine treatment causes less severe and less frequent systemic reactions than specific desensitization.

In the course of several thousand injections of histamine we have encountered systemic reactions in a few instances only. On one occasion a patient suffering from vasomotor rhinitis developed very severe headache two to three hours after the injection of .33 gamma. The headache lasted for about eighteen hours. In another case of vasomotor rhinitis the injection of 1 gamma brought on a severe attack of urticaria, which started at the site of the injection and persisted for several days. Two other patients, during the course of preseasonal treatment for hay fever, developed mild angioneurotic edema of the eyelids on several occasions after the injection of small amounts of histamine, and one of these patients on another occasion had urticaria. In view of these comparatively rare and not very severe systemic reactions, we feel that histamine would be indicated in such cases in which the patients react strongly to specific desensitization.

We have treated 105 persons with histamine. Sixty patients were suffering from asthma, vasomotor rhinitis, or both; their symptoms were

in most instances due to allergens other than pollens. The results of this treatment have been very satisfactory in a considerable percentage of the cases. In some instances the patients were not at all benefited. We were especially impressed by the fact that a number of patients suffering from severe asthma of long standing, and who had received specific desensitization treatment at the hands of very capable allergists, were greatly improved by histamine treatment.

I would like to present two successfully treated patients:

1) The patient, a six-year old girl, had had asthmatic attacks since she was fifteen months old. The attacks were especially severe during the winter; however, the patient had also occasional attacks during the summer months. During the last years the attacks had become more frequent and much more severe. The child had been laid up with asthma almost the entire winter of 1938 to 1939. The asthmatic attacks usually followed a head-cold. During August and September 1939 she had frequent attacks of urticaria. We first saw the patient last September. The physical examination was essentially negative. Skin-tests showed positive reactions to house-dust, cottonseed, ragweed and various grass pollens. Histamine treatment was started at the end of September. The initial injection in this case was .005 gamma. The dosage was increased very slowly and the injections were given throughout the fall and winter. The child had several colds during the course of the winter, and on one single occasion she had a very mild asthmatic attack, which lasted for a few hours only. The patient was last seen a few days ago; the dosage at this time was 15 gammas. The child's general physical condition is greatly improved; incidentally, she has gained ten pounds during the course of treatment.

2) The following case, which we had the opportunity of observing, represents, in our opinion, a direct experimental proof of the correctness of the histamine theory. The patient, a thirty-six year old baker, had been suffering from severe vasomotor rhinitis for the past three years. His attacks of paroxysmal sneezing and profuse watery nasal discharge occurred only in the bakeshop and only when he worked with wheat flour. The attacks would last for many hours. The patient gave a strong positive skin reaction to wheat extract. Histamine treatment was started with .1 gamma at the end of February 1938. Decided improvement was noted after the eleventh injection, which amounted to 3 gammas. Improvement continued and the patient was able to work without any

symptoms of rhinitis in April, May and June, during which time he was receiving injections of histamine. The last injection of 40 gammas was given at the beginning of July. The patient was able to work during the entire summer and had only infrequent, very mild symptoms. When we saw him in September he had been sneezing more frequently for about one week. He was given four injections of histamine and did not return for treatment, as he was improved. In July 1939, that is three-quarters of a year later, the patient reported that he had been working steadily with wheat flour since November 1938. He had been free from allergic symptoms during the entire time.

We have further treated persons with seasonal hay fever. Some of these patients received two or three courses of treatment with histamine during consecutive years. The results of this treatment during 1938 and 1939 are the following: Of a total of 48 patients, 21 were treated with very good, 12 with fair results; 15 patients had no benefit from the treatment.

From a theoretical point of view we are especially interested in the results achieved in hay fever as we are here dealing with a condition in which the clinical picture is usually clear cut, in which there are rarely complicating factors as in bronchial asthma, and in which the causative allergen can generally be ascertained with good precision. We are aware of the fact that the percentage of hay fever cases benefited by histamine treatment is not as large as that of cases receiving specific desensitization. This, we feel, is due to our not yet knowing the optimal dosage. The length of time we have been using histamine is short and one must consider how long it took to develop the optimal dosage for specific desensitization. At this stage we believe the essential point to be the fact that *qualitative* results can be achieved with histamine in the treatment of hay fever, which compare absolutely with those achieved with specific desensitization.

In our opinion histamine therapy is destined to mark a further advance in the treatment of allergic diseases. Much experience will be needed before a final verdict can be given, and it has been the objective of this presentation to stimulate other workers to help procure it.

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